NIH Biographical Sketch Common Form

Name: Dohlman, Henrik Gunnar

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0003-2443-0729

Position Title: Professor

Organization and Location:University of North Carolina, Chapel Hill, North Carolina, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
University of California Berkeley, Berkeley, California, United States	Not applicable (N/A)	10/1989	02/1993	Molecular and Cell Biology
Duke University, Durham, North Carolina, United States	Not applicable (N/A)	01/1989	09/1989	Cardiology
Duke University, Durham, North Carolina, United States	Doctor of Philosophy (PHD)	08/1982	12/1988	Biochemistry

Appointments and Positions

2016 - present Professor and Chair, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States
2016 - present Professor and Chair, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States
2001 - present Professor, University of North Carolina, Chapel Hill, North Carolina, United States
1993 - 2001 Professor, Yale University, New Haven, Connecticut, United States

Products

Products Closely Related to the Proposed Project

1. Knight KM, Krumm BE, Kapolka NJ, Ludlam WG, Cui M, Mani S, Prytkova I, Obarow EG, Lefevre TJ, Wei W, Ma N, Huang XP, Fay JF, Vaidehi N, Smrcka AV, Slesinger PA, Logothetis DE, Martemyanov KA, Roth BL, Dohlman HG. A neurodevelopmental disorder mutation locks G proteins in the transitory pre-activated state. Nat Commun. 2024 Aug 5;15(1):6643. PubMed Central PMCID: PMC11300612.
2. Knight KM, Obarow EG, Wei W, Mani S, Esteller MI, Cui M, Ma N, Martin SA, Brinson E, Hewitt N, Soden GM, Logothetis DE, Vaidehi N, Dohlman HG. Molecular annotation of G protein variants in a neurological disorder. Cell Rep. 2023 Dec 26;42(12):113462. PubMed Central PMCID: PMC10872635.
3. Hewitt N, Ma N, Arang N, Martin SA, Prakash A, DiBerto JF, Knight KM, Ghosh S, Olsen RHJ, Roth BL, Gutkind JS, Vaidehi N, Campbell SL, Dohlman HG. Catalytic site mutations confer multiple states of G protein activation. Sci Signal. 2023 Feb 14;16(772):eabq7842. PubMed Central PMCID: PMC10021883.
4. Knight KM, Ghosh S, Campbell SL, Lefevre TJ, Olsen RHJ, Smrcka AV, Valentin NH, Yin G, Vaidehi N, Dohlman HG. A universal allosteric mechanism for G protein activation. Mol Cell. 2021 Apr 1;81(7):1384-1396.e6. PubMed Central PMCID: PMC8026646.
5. Isom DG, Dohlman HG. Buried ionizable networks are an ancient hallmark of G protein-coupled receptor activation. Proc Natl Acad Sci U S A. 2015 May 5;112(18):5702-7. PubMed Central PMCID: PMC4426463.

Other Significant Products Highlighting Contributions to Science

1. Dixon RA, Kobilka BK, Strader DJ, Benovic JL, Dohlman HG, Frielle T, Bolanowski MA, Bennett CD, Rands E, Diehl RE, Mumford RA, Slater EE, Sigal IS, Caron MG, Lefkowitz RJ, Strader CD. Cloning of the gene and cDNA for mammalian beta-adrenergic receptor and homology with rhodopsin. Nature. 1986 May 1-7;321(6065):75-9. PubMed PMID: 3010132.
2. Dohlman HG, Apaniesk D, Chen Y, Song J, Nusskern D. Inhibition of G-protein signaling by dominant gain-of-function mutations in Sst2p, a pheromone desensitization factor in Saccharomyces cerevisiae. Mol Cell Biol. 1995 Jul;15(7):3635-43. PubMed Central PMCID: PMC230601.
3. Slessareva JE, Routt SM, Temple B, Bankaitis VA, Dohlman HG. Activation of the phosphatidylinositol 3-kinase Vps34 by a

G protein alpha subunit at the endosome. Cell. 2006 Jul 14;126(1):191-203. PubMed PMID: 16839886; NIHMSID: NIHMS433844.

4. Cappell SD, Baker R, Skowyra D, Dohlman HG. Systematic analysis of essential genes reveals important regulators of G protein signaling. Mol Cell. 2010 Jun 11;38(5):746-57. PubMed Central PMCID: PMC2919228.
5. Hao N, Nayak S, Behar M, Shanks RH, Nagiec MJ, Errede B, Hasty J, Elston TC, Dohlman HG. Regulation of cell signaling dynamics by the protein kinase-scaffold Ste5. Mol Cell. 2008 Jun 6;30(5):649-56. PubMed Central PMCID: PMC2518723.

Certification:

I certify that the information provided is current, accurate, and complete. This includes but is not limited to information related to domestic and foreign appointments and positions.

I also certify that, at the time of submission, I am not a party to a malign foreign talent recruitment program.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§ 287, 1001, 1031 and 31 U.S.C. §§ 3729-3733 and 3802.

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NIH BIOGRAPHICAL SKETCH SUPPLEMENT

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Personal Statement

My overall **research** goal is to identify new regulators of G protein signaling and desensitization.

As a graduate student with Robert Lefkowitz, I coauthored a paper describing the first molecular cloning and sequencing of a G protein-coupled receptor (GPCR) (Dixon et al., Nature 1986). GPCRs respond to two-thirds of all hormones and neurotransmitters, as well as sensory signals, and are the target of one third of all pharmaceuticals. As a post-doc with Jeremy Thorner I initiated molecular genetic studies of G protein signaling in yeast. My independent lab has since been conducting large-scale genomic, proteomic, and metabolomic analysis to identify mutants with altered signaling and desensitization properties. These mutants are then characterized biochemically in yeast and animal cells. This effort led to the identification of the first RGS protein (Dohlman et al., Molecular and Cell Biology 1995). RGS proteins inactivate G proteins by accelerating their intrinsic GTPase activity. Thus, past contributions include identification of the first G protein activator and inactivator.

Our investigations of desensitization have included novel post-translational modifications. My lab was the first to use mass spectrometry to map a site of protein ubiquitination in vivo (for Gα, in 2002), and the first to demonstrate signaling by G proteins at endosomes (Slessareva et al., Cell 2006). Thus, past contributions include ubiquitin-mediated trafficking to, and signaling at, endomembrane compartments.

A major **training** goal has been to mentor young scientists. I have consistently strived to recruit and maintain a multi-dimensional scientific team, which I believe will bring new ideas and new directions to the scientific endeavor. Including current members of the lab, I have sponsored more than 50 postdoc and doctoral students and nearly as many undergraduates, and continue to support their careers in the biomedical research workforce. I am an instructor in UNC's Responsible Conduct in Research course, which provides training in rigorous and reproducible experimental design, methodology, analysis, interpretation and reporting of results. In 2019 my efforts were recognized by the UNC Office of Graduate Education award for "Excellence in Basic Science Mentoring."

My **leadership** experience has helped me to become a better scientist and a better mentor. As past Director of Graduate Studies I revamped existing course requirements and implemented an accelerated timeline to graduation, including a much earlier submission of the thesis research proposal. As past Director of the department's Grant Writing course, designed to prepare students for the qualifying exam and for NIH grant submissions, I wrote a 60+ page course manual, which I have shared freely with other departments and institutions. As department Chair I have led RCR training focusing on plagiarism and image manipulation, and taken initiatives to improve broader educational access and to address mental health concerns.

As a long-standing member of the scientific community, I have served as Chair of the Molecular Pharmacology division of ASPET, Chair of a Gordon Research Conference, Co-organizer of the first ASPET meeting on RGS proteins, Deputy Editor for the Journal of Biological Chemistry, and service on NIH grant review panels.

Honors

2023	Fellow, American Society for Pharmacology and Experimental Therapeutics
2021	Fellow, American Society for Biochemistry and Molecular Biology
2019	Excellence in Basic Science Mentoring Award , University of North Carolina at Chapel Hill
2011	Fellow, American Association for the Advancement of Science

Contributions to Science

1. As a graduate student, I contributed to the genetic identification of the beta2-adrenergic receptor, the first of the large and pharmacologically important family of G protein-coupled neurotransmitter receptors (Dixon et al., Nature 1986). That work

was cited in the 2012 Nobel Prize to Robert Lefkowitz.

2. In 1995 I described the first of a new family of desensitization factors, called RGS proteins (Dohlman et al., Molecular and Cell Biology 1995). Whereas receptors activate G proteins, RGS proteins inactivate G proteins, and do so by accelerating their GTPase activity. Human genetic studies have since revealed that RGS proteins are necessary for desensitization to light and other stimulants.
3. More recently, we identified a number of new signaling and desensitization mechanisms. These findings include G protein signaling from an internal (endomembrane) compartment (Slessareva et al. Cell 2006), the development of microfluidics methods and mathematical models to follow signaling in time and space (Hao et al., Molecular Cell 2008), identification of new pathway regulators from a comprehensive screen of the essential genome (Cappell et al., Molecular Cell 2010), and allosteric regulation of G protein signaling (Isom et al., PNAS 2015; Knight et al., Molecular Cell 2021). Newly discovered regulators have been characterized using integrated genetic, biochemical, computational, cell biological (including microfluidics and electron microscopy) and biophysical (including mass spectrometry, x-ray crystallography and NMR) approaches.
4. Not surprisingly, mutations in G proteins are responsible for disease; the best-known examples are uveal melanoma and developmental epileptic encephalopathies. A detailed cellular and molecular analysis of disease-linked G protein mutations has led to conceptual breakthroughs with broad implications for future therapeutics. First, we have shown that some disease mutations impose an ensemble of conformational states on the G protein α subunit, and these states differ among the four major subclasses of Gα subtypes (Hewitt et al., Science Signaling 2023). Following a screen of 55 unique mutations in Gαo, all linked to epileptic encephalopathies, we identified several that block or lock key steps of the G protein activation cycle (Knight et al., Cell Reports 2023). Most of the mutations act at a distance, by imposing or disrupting important allosteric communication networks. Our recent studies support our hypothesis that this is not one, but at least four, distinct conditions, each with a different mechanism of action. Mutants in Group 1 are nucleotide-free and form a nonproductive complex with receptors and Gβγ (Knight et al., Nature Communications 2024). Group 2 mutants bind stably to Gβγ, even when loaded with GTP (Knight et al., Molecular Cell 2021). Many Group 3 mutants appear unable to bind RGS proteins, leading to sustained release of Gβγ. The remaining mutants are unstable and unable to bind to and sequester Gβγ.
5. The integration of human genetics, computational biology, biochemistry, and cell biology will be increasingly important in biomedical research, and these efforts represent an important training opportunity for my students and postdoctoral fellows.

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